Citation:

Halton TL, Willett WC, Liu S, Manson JE, Albert CM, Rexrode K, Hu FB. Low-carbohydrate-diet score and the risk of coronary heart disease in women. *N Engl J Med.* 2006 Nov 9;355(19):1991-2002.

PubMed ID: 17093250

Study Design:

Prospective Cohort Study

Class:

B - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To examine prospectively the association between the low-carbohydrate diet score and the risk of coronary heart disease in the Nurses' Health Study cohort.

Inclusion Criteria:

- Participants from the Nurses' Health Study who completed a validated food frequency questionnaire

Exclusion Criteria:

- All women at baseline who left 10 or more food items blank or had implausibly high (>3500 kcal) or low (<500 kcal) daily energy intakes on the food frequency questionnaire
- Women with a history of diabetes, cancer or other cardiovascular disease before 1980, because these diagnoses may cause alterations in diet

Description of Study Protocol:

Recruitment

- Nurses' Health Study initiated in 1976, when 121,700 female registered nurses aged 30 - 55 years completed a mailed questionnaire

Design: Prospective cohort study

Blinding used (if applicable): not applicable

Intervention (if applicable): not applicable

Statistical Analysis

- Women were divided into 10 categories based on their low-carbohydrate diet score
- To represent long-term intake and reduce measurement error, the cumulative average low-carbohydrate diet score was calculated based on the 1980, 1984, 1986, 1990, 1994 and 1998 questionnaires
- Incidence rates for coronary heart disease were calculated by dividing cases by the person-years of follow-up for each decile of the low-carbohydrate diet score
- Relative risks of coronary heart disease were calculated by dividing the rate of occurrence of coronary heart disease in each decile by the rate in the first (lowest) decile
- Cox proportional hazards models were used to adjust for potentially confounding variables

Data Collection Summary:

Timing of Measurements

- Since 1976, information on disease status and lifestyle factors has been collected from the cohort every 2 years
- Dietary intake measured in 1980, 1984, 1986, 1990, 1994 and 1998
- Coronary heart disease assessed over 20 years of follow-up

Dependent Variables

- Risk of coronary heart disease assessed through follow-up questionnaire responses and examination of medical records
- Deaths were identified from state vital records and the National Death Index or reported by the participants' next of kin or the United States Postal Service

Independent Variables

- Low-carbohydrate diet score: data from a semiquantitative food frequency questionnaire were used to calculate a low-carbohydrate diet score, which was based on the percentage of energy as carbohydrate, fat and protein (higher scores reflect a higher intake of fat and protein and a lower intake of carbohydrate)
- Study participants were divided into 11 strata of fat, protein and carbohydrate intake expressed as a percentage of energy
- 1980 food frequency questionnaire included 61 food items, and was revised in 1984 to include twice as many
- Nutrient values were computed; all food composition values obtained from Harvard University food composition database

Control Variables

- Parental history of myocardial infarction
- Postmenopausal hormones
- Smoking status
- Body weight
- Aspirin use
- Physical activity

Description of Actual Data Sample:

Initial N: 98,462 women completed the 1980 questionnaire

Attrition (final N): 82,802 women

Age: aged 30 - 55 years at baseline

Ethnicity: not reported

Other relevant demographics:

Anthropometrics

Location: United States

Summary of Results:

Key Findings

- During 20 years of follow-up, there were 1994 new cases of coronary heart disease documented
- After multivariate adjustment, the relative risk of coronary heart disease comparing highest and lowest deciles of the low-carbohydrate diet score was 0.94 (95% confidence interval: 0.76 - 1.18, P for trend = 0.19).
- The relative risk comparing highest and lowest deciles of a low-carbohydrate diet score on the basis of the percentage of energy from carbohydrate, animal protein and animal fat was 0.94 (95% confidence interval: 0.74 - 1.19, P for trend = 0.52), whereas the relative risk on the basis of the percentage of energy from intake of carbohydrates, vegetable protein and vegetable fat was 0.70 (95% confidence interval: 0.56 - 0.88, P for trend = 0.002).
- A higher glycemic load was strongly associated with an increased risk of coronary heart disease (relative risk comparing highest and lowest deciles = 1.90, 95% confidence interval: 1.15 - 3.15, P for trend = 0.003).

Other Findings

- The cumulative average low-carbohydrate diet score ranged from a median of 5.0 in the first decile to a median of 26.0 in the tenth decile
- Women who had a higher score were more likely to smoke and had a higher BMI, a lower dietary glycemic load, a lower caloric intake, and a higher intake of saturated fat
- BMI increased by approximately 2.5 units from baseline to the end of follow-up, regardless of the low-carbohydrate diet score
- Data on lipid levels were available for a subgroup of 466 participants: low-carbohydrate diet score was not associated with total cholesterol, HDL cholesterol or LDL cholesterol but was inversely associated with triglyceride level (P for trend = 0.05).

Author Conclusion:

In conclusion, diets lower in carbohydrate and higher in protein and fat were not associated with an increased risk of coronary heart disease in this cohort of women. When vegetable sources of fat and protein were chosen, these diets were related to a lower risk of coronary heart disease.

Reviewer Comments:

Cohort consisted of female registered nurses. Dietary intake measured several times during 20 years of follow-up. Low-carbohydrate diet scoring system devised by authors. Authors note that the amount of carbohydrate in the highest category of carbohydrate intake in the cohort was similar to that consumed by participants in the clinical trials of low carbohydrate diets.

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions		
1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes

Validity Questions		
1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**	Yes

3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	Yes
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	N/A
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	Yes
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	Yes
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	N/A
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	Yes
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A

6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	N/A
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	N/A
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes

	8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
	8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
	8.6.	Was clinical significance as well as statistical significance reported?	Yes
	8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**		Yes
	9.1.	Is there a discussion of findings?	Yes
	9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**		Yes
	10.1.	Were sources of funding and investigators' affiliations described?	Yes
	10.2.	Was the study free from apparent conflict of interest?	Yes